Bull. Inst. Chem. Res., Kyoto Univ., Vol. 65, No. 3, 1987

Regioselective Hydroxylation in the C Ring of *ent*-Kaurene; Syntheses of *ent*-11α-Hydroxykaurene and *ent*-11α-Hydroxykauren-15-one

Manabu NODE*, Tetsuya KAJIMOTO**, Eiichi FUJITA***
and Kaoru FUJI*

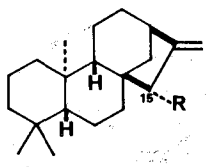
Received May 30, 1987

Regioselective hydroxylation at the C–11 position of *ent*-kaurene (**5**) was achieved *via* radical cyclization of the hydroxy group at the C–17 position. Naturally occurring *ent*-11α-hydroxykauren-15-one (**3**) was synthesized from the hydroxylated kaurene **4** in two steps.

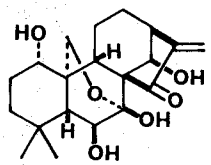
KEY WORDS: Hydroxylation/ *ent*-Kaurene/ *ent*-11α-Hydroxykaurene/ *ent*-11α,15β-Dihydroxykaurene/ *ent*-11α-Hydroxykauren-15-one/ Radical Cyclization/ Lead Tetraacetate/ Tosylhydrazone/

In the course of our investigation on the physiologically active diterpenoids, we found that *ent*-15β-hydroxykaur-16-ene (**1**) had a potent stimulating effect on corticosterone production in isolated rat adrenal cells[1] and that poly hydroxylated kaurenoids such as oridonin (**2**) showed strong antitumor activity against Ehrlich asites carcinoma in mice.[2] These findings stimulated our interset into investigating the steroidogenic effect of various hydroxykaurenes and the antitumor effect of various hydroxykaurenones, because it is anticipated that the hydroxy group in the kaurene skeleton plays an important role in the action of physiologically active kaurenoids.

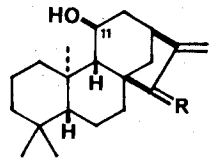
In oder to prepare various hydroxykaurenoids, we recently succeeded in regioselective hydroxylations of the unactivated carbon atoms (C–7, –9, –12 and –14) on the B and C rings in the kaurene skeletone through radical cyclization of a hydroxymethyl group on the D ring.[3] Though a report concerning the hydroxylation of the C–11 position on the kaurene has already been published by Kato and coworkers,[4] the synthetic method for the preparation of *ent*-11α-hydroxykauren-15-one (**3**) by Kato requires comparatively long synthetic steps (total 11 steps



1 ; R = OH
5 ; R = H



2

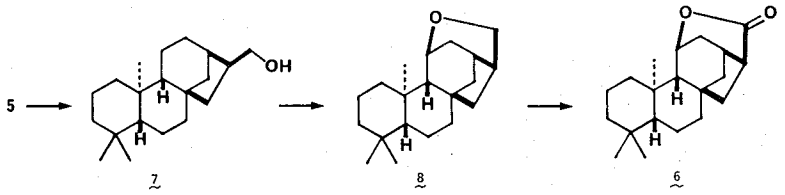


3 ; R = O
4 ; R = H_2

* 野出 学, 冨士 薫 : Institute for Chemical Research, Kyoto University, Uji, Kyoto 611.
** 梶本哲也 : Faculty of Pharmaceutical Sciences, Kumamoto University, 5–1 Oe-honmachi, Kumamoto 862.
*** 藤田榮一 : Osaka University of Pharmaceutical Science, 10–65 Kawai 2-Chome, Matsubara 580.

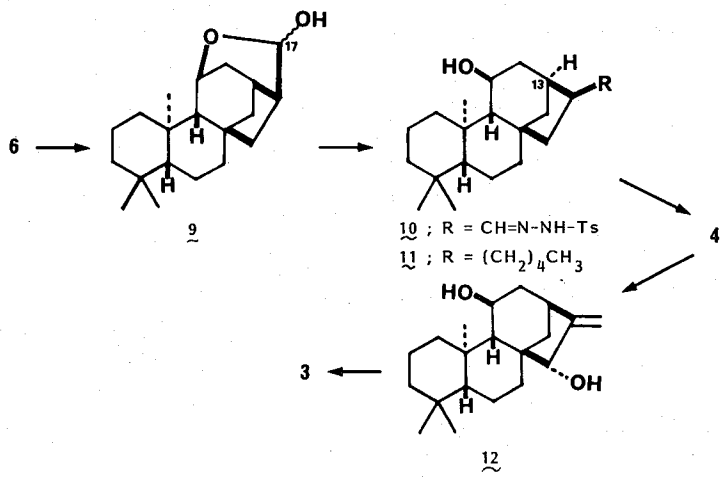
from kaurene). No report on the synthesis of *ent*-11α-hydroxykaurene (**4**) has appeared to date. Here we report the convenient short syntheses of *ent*-11α-hydroxykauren-15-one (**3**) and *ent*-11α-hydroxykaurene (**4**) from *ent*-kaurene (**5**).

A method for the transformation of kaurene (**5**) into the lactone **6** was published by McCrindle[5] and Kato,[4] respectively (Scheme I). However, radical cyclization of the alcohol **7** into the cyclic ether **8** proceeded in a yield of less than 41% according to thier method. The yield was improved to 80% by the use of the modified reaction conditions (See experimental section).



Scheme I

The transformation of the lactone **6** into the hydroxykaurenone **3** *via* **4** is shown in Scheme II. Thus, reduction of the lactone **6** with diisobutyl aluminum hydride gave a mixture of epimeric hemiacetals **9**, which was converted to the tosylhydrazone **10** in 70% overall yield by the treatment with tosylhydrazone in the presence of acetic acid. The configuration of hydrazone moiety in the structure of **10** was considered to be a β-configuration because the torsional strain between the 13-hydrogen and the 17-carbon atom[6] prevents the inversion of the configuration from β to α under the reaction conditions. The attempted Shapiro reaction[7] on the hydrazone **10** with n-butyl lithium (execss) did not afford the desired kaurenol **4**, but the butylated product **11**.[8] On the other hand, use of lithium diisopropylamide which is a non-nucleophilic base gave the intended product **4** in low yield (16%). Several non-nucleophilic bases were tried to improve the yield without success.



Scheme II

Allylic oxidation of kaurenol **4** by Sharpless method[9] proceeded smoothly to give dihydroxykaurene **12** resulting from the less hindered α-side attack of the reagent. Subsequent oxidation of the allylic alcohol **12** with manganese dioxide afforded the α,β-unsaturated ketone **3**, which was identified with naturally occuring *ent*-11α-hydroxykauren-15-one[10] by the comparison of the spectroscopic data.

Investigation of the physiological activity of synthesized 11-hydroxykaurene and its derivatives is now in progress.

EXPERIMENTAL SECTION

Infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer or a JASCO A-202 spectrophotometer, and ^{1}H-NMR spectra were obtained with JEOL FX-400 spectrometer. Chemical shift are reported relative to internal tetramethylsilane. Mass spectra (MS) were determined on a JEOL JMS-O1SG double-focusing mass spectrometer or a JEOL JMS-DX 300 mass spectrometer. Melting points were determined with a Yanagimoto apparatus and are uncorrected.

ent-kaurene (**5**) isolated from the leaves of *Cryptomeria japonica*[11] was converted to the kauranol **7** by the hydroboration-oxidation reaction.[12]

Radical Cyclization of Kauranol 7 with Lead Tetraacetate

A solution of **7** (301 mg) and lead tetraacetate (12.5 g) in dry cyclohexane was stirred with refluxing under irradiation with 100 W tungsten lamp until kauranol on TLC disappeared (ca. 2.5 h). After filtration, the residue was washed with ether. The combined organic layer was washed with aqueous sodium thiosulfate and brine successively. After being dried over Na_2SO_4, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel column to give the cyclic ether **8** (249 mg, 80% yield).[5]

ent-(16R)-Kauran-17,11α-olide (6)

To a solution of **8** (4.51 g) in a mixture of carbon tetrachloride (35 ml) and acetonitrile (35 ml) were added aqueous sodium periodate (13.5 g in 50 ml water) and ruthenium trichloride (32 mg). The mixture was vigorously stirred for 2.5 h at room temperature. After being quenched with *iso*-propanol to destroy remaining RuO_4, the reaction mixture was diluted with water. The extract with dicholromethane was treated as usual to give a crude product, which was chromatographed on silica gel column to afford lactone **6**[5] (4.25 g, 90% yield), mp 177-178°C.

Tosylhydrazone 10

To a solution of **6** (45.8 mg) in dry tetrahydrofuran (2.5 ml) was added hexane solution (2.5 ml) of 20% diisobutylaluminium hydride, and the mixture was stirred for 1 h at 0°C. After being quenched with water, the reaction mixture was filtered with celite. The filtrate was evaporated to give a crude crystalline product (72 mg) which contained epimeric mixture of **9**. To a solution of the crude **9** dissolved in dichloromethane (1 ml) and acetic acid (1 ml) was added tosylhydrazone (83 mg) and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was then poured into cold aqueous solution of sodium bicarbonate. Usual

work up including extraction with ethyl acetate gave a crude material (126.5 mg) which was chromatographed on the silica gel column to yield tosylhydrazone **10** (50.7 mg, 70%), colorless powder from hexane — ethyl acetate, mp 161.5–162.5°C. IR ν_{max} cm^{-1} ($CHCl_3$): 3320, 1714 and 1610. ^{1}H-NMR δ ($CDCl_3$): 7.81, 7.30 (each 2H, q of AB type, J=8 Hz, Aromatic-H), 6.40 (1H, s, N–H), 4.26 (1H, d, changed to singlet by D_2O, J=11 Hz, 11–H), 4.06 (1H, s, 17–H), 3.85 (1H, d, J=11 Hz, –O*H*), 2.43 (3H, s, Ar–CH_3), 0.92, 0.85 and 0.81 (each 3H, s, 3×CH_3), Anal. Calcd for $C_{27}H_{40}O_3N_2S$: C, 68.61; H, 8.51; N, 5.93. Found: C, 68.93; H, 8.65; N, 5.91.

Shapiro Reaction with Tosylhydrazone 10

To a solution of **10** (20.3 mg) in dry ether (1.5 ml) was added *n*-butyl lithium (1.5 M THF solution, 0.25 ml) and the mixture was stirred at room temperature for 1 h. Usual work up of the extract gave a crude substance which was chromatographed on the silica gel column to give butyulated compound **11** (10.1 mg, 67%) as oil. IR ν_{max} cm^{-1} ($CHCl_3$): 3600, 3450, 1455, 1395 and 965. ^{1}H-NMR δ ($CDCl_3$): 3.86 (1H, d, J=6.6 Hz, 11–H), 2.03 (1H, m), 0.88, 0.85 and 0.78 (each 3H, s, 3×CH_3). High-resolution MS *m/z*; M^+ Calcd for $C_{24}H_{42}O$: 346.3234. Found: 346.3233.

***ent*-11α-Hydroxykaurene (4)**

To a solution of tosylhydrazone **10** (23.1 mg) in dry ether (1 ml) was added an ether solution of lithium diisopropylamid (0.75 M, 0.5 ml) and the mixture was stirred at room temperature for 1.5 h. Usual work up of the extract gave a crude substance, which was chromatographed on the silica gel column to separate kaurenol **4** (2.3 mg, 16%), colorless powder from methanol — ethy acetate, mp 131–132°C. ^{1}H-NMR δ ($CDCl_3$): 5.03, 4.85 (each 1H, s, 17–H_2), 3.87 (1H, br s, 11–H), 2.70 (1H, br s, 13–H), 0.90, 0.88 and 0.81 (each 3H, s, 3×CH3). MS *m/z*; 288 (M^+), and 270 (M^+–H_2O).

***ent*-11α,15β-Dihydroxykaurene (12)**

To a solution of SeO_2 (11.0 mg) in CH_2Cl_2 (1 ml) was added 75 μl of 70% aqueous *tert*-butyl hydroperoxide. After the mixture had been stirred for 1 h at room tepmperature, a solution of kaurenol **4** (50 mg) in dicholromethane (3 ml) was added and the mixture was stirred for 1.5 h at room temperature. After being quenched with aqueous sodium thiosulphate, usual work up of the extract gave an oily substance (70.8 mg), which was chromatographed on a silica gel column to give diol **12** (38 mg, 76%), colorless needles (from hexane). mp 192.5–193.2°C. IR ν_{max} cm^{-1}: 3650. ^{1}H-NMR δ ($CDCl_3$): 5.27, 5.25 (each 1H, s, 17–H_2), 4.26 (1H, s, 15–H), 3.88 (1H, d, J=5.1 Hz, 11–H), 2.78 (1H, br s, 13–H), 0.92, 0.89 and 0.82 (each 3H, s, 3×CH_3). High-resolution MS *m/z*; M^+ Calcd for $C_{20}H_{32}O_2$: 304.240. Found: 304.238.

***ent*-11α-Hydroxykauren-15-one (3)**

To a solution of **12** (9.2 mg) in CH_2Cl_2 (1 ml) was added maganese dioxide (49.8 mg) and the mixture was stirred for 3 days at room temperature. After filtration, the residue was washed with dichloromethane. The combined solution was evaporated off to give a residue which was chromatographed on a silica gel column to separate crystalline ketone **3** (3.4 mg,

37%).

The obtained ketone **3** was identified as *ent*-11α-hydroxykauren-15-one[10] by the comparison of the IR and ^{1}H-NMR data.

REFERENCES AND NOTES

(1) K. Moriwaki, M. Gomi, Y. Itoh, S. Iida, M. Tsugawa, S. Tarui, K. Fuji, M. Node and T. Kajimoto, *Life Science,* 1986, **38**, 453.

(2) E. Fujita, Y. Nagao, M. Node, K. Kaneko, S. Nakazawa and H. Kuroda, *Experientia,* 1976, **32**, 203; E. Fujita, Y. Nagao, K. Kaneko, S. Nakazawa and H. Kuroda, *Chem. Pharm. Bull.,* 1976, **24**, 2118; E. Fujita, Y. Nagao, T. Kohno, M. Matsuda and M. Ozaki, *Chem. Pharm. Bull.,* 1981, **29**, 3208; M. Node, M. Sai, K. Fuji, E. Fujita, S. Takeda and N. Unemi, *Chem. Pharm. Bull.,* 1983, **31**, 1433; K. Fuji, M. Node, N. Ito, E. Fujita, S. Takeda and N. Unemi, *Chem. Pharm. Bull.,* 1985, **33**, 1038.

(3) M. Node, T. Kajimoto, K. Nishide, E. Fujita and K. Fuji, *Tetrahedron Lett.,* 1984, **25**, 219; M. Node, T. Kajimoto, N. Ito, J. Tamada, E. Fujita and K. Fuji, *J. Chem. Soc., Chem. Commun.* 1986, 1165.

(4) N. Fukazawa, M. Funamizu, Y. Kitahara and T. Kato, *Chem. Lett.,* 1976, 1253.

(5) A. J. McAlees and R. McCrindle, *Can. J. Chem.,* 1973, **51**, 4103.

(6) J. MacMillan and E. R. H. Walker, *J. C. S. Perkin I,* 1972, 986.

(7) For an extensive review, R. H. Shapiro, *Org. React.,* 1976, **23**, 405.

(8) In the reaction of tosylhydrazone with alkyllithium, substitution occasionally competes with elimination (see ref. 7).

(9) M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.,* 1977, **99**, 5526.

(10) J. D. Connolly and M. S. Thornton, *J. C. S. Perkin I,* 1973, 736.

(11) R. A. Appleton, R. McCrindle and K. H. Overton, *Phytochemistry,* 1968, **7**, 135.

(12) J. R. Hanson, *Tetrahedron,* 1967, **73**, 801.